REMARKS

Reconsideration and withdrawal of the requirement for election of species and rejections of the application respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 84-118 are pending in this application. Non-elected claims 119-220 have been cancelled and claim 84 has been amended. Applicants reserve the right to pursue the subject matter of cancelled claims in continuing application. Support for claim 84 is found on page 6, lines 29-33 of the specification as originally filed. No new matter has been added by this amendment.

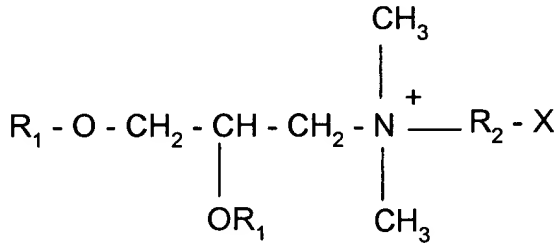
It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. THE REJECTIONS UNDER 35 U.S.C. §103 ARE OVERCOME

Claims 84, 85 and 118 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cox et al. (J. Virol. Vol. 67, pages 5664-5667; IDS reference AT) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999). Claims 84-91 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cox et al. (J. Virol. Vol. 67, pages 5664-5667; IDS reference AT) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733). Claims 84, 92, 94, 100 and 104 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cox et al. (J. Virol. Vol. 67, pages 5664-5667; IDS reference AT) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945). Claims 84, 93 and 104 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cox et al. (J. Virol. Vol. 67, pages 5664-5667; IDS reference AT) in view of Klavinskis et al. (J. Immunol.

Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240). Claims 84-95, 100-111 and 118 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cox et al. (J. Virol. Vol. 67, pages 5664-5667; IDS reference AT) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733), Li (WO 96/40945) and Choi et al. (Virology 1998, 250:230-240). These rejections are addressed collectively and are respectfully traversed.

The present invention provides a DNA vaccine against a bovine pathogen comprising at least one plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding an immunogen of the bovine pathogen, wherein the bovine pathogen is BRSV, BVDV-1, BVDV-2 or bPI-3, and a cationic lipid containing a quaternary ammonium salt, of the formula



in which R_1 is a saturated or unsaturated linear aliphatic radical having 12 to 18 carbon atoms, R_2 is an aliphatic radical containing 2 or 3 carbon atoms, and X a hydroxyl or amine group.

The lipid can be DMRIE and the vaccine can further comprise DOPE. The vaccine can also further comprise bovine or porcine GM-CSF, or an expression vector that contains and expresses in a porcine host cell a nucleotide sequence encoding porcine GM-CSF, or an expression vector that contains and expresses in a bovine host cell a nucleotide sequence encoding porcine GM-CSF, wherein this additional expression vector can be a plasmid.

The nucleotide sequence encoding the immunogen can have deleted therefrom a portion encoding a transmembrane domain, and the plasmid can further contain and express in a a nucleotide sequence encoding a heterologous tPA signal sequence, such as a human tPA signal sequence. Even further, the plasmid can further contain a stabilizing intron, such as intron II of a rabbit beta-globin gene.

None of the cited documents teaches or suggests a DNA vaccine that comprises, *inter alia*, a plasmid that expresses DNA encoding an immunogen of a bovine pathogen, wherein the

bovine pathogen is BRSV, BVDV-1, BVDV-2 or bPI-3. Cox relates to the bovine pathogen BHV-1. Cox does not teach or suggest other bovine pathogens, such as BRSV, BVDV-1, BVDV-2 or bPI-3. Klavinskis does not teach or suggest bovine pathogens of BRSV, BVDV-1, BVDV-2 or bPI-3. Xiang, Baker, Li and Choi do not cure the deficiencies of Cox or Klavinskis. Accordingly, in view of the herein arguments and the accompanying references, reconsideration and withdrawal of the 35 U.S.C. §103 rejection are respectfully requested.

III. THE DOUBLE-PATENTING REJECTIONS ARE OVERCOME

Claims 84-118 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 4, 5 and 16-19 of copending Application No. 09/766,442.

The issue of whether there is indeed double patenting is contingent upon whether new claims herewith are indeed considered and entered; and, if so, whether the Examiner believes there is overlap with claims ultimately allowed in the co-pending application. If upon agreement as to allowable subject matter it is believed that there is still a double patenting issue, then, at that time, if indeed necessary, a Terminal Disclaimer as to co-pending U.S. Application No. 09/766,442 will be filed.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

Claims 84, 85, 96, 112 and 116-118 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 ("the '473 patent") in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999). Claims 84-91 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent" in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733). Claims 84, 92, 94, 95, 100 and 108 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent" in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages

254-262; January 1, 1999) and further in view of Li (WO 96/40945). Claims 84, 93, 97, 98 and 104 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent" in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240). Claims 84- 118 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent" in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733), Li (WO 96/40945) and Choi et al. (Virology 1998, 250:230-240). These rejections are addressed collectively and are respectfully traversed.

There is no teaching or suggestion in the '473 patent to combine a DNA vaccine with a cationic lipid containing a quaternary ammonium salt and having the indicated formula. Furthermore, the Office Action admits that the '473 patent does not teach that the vaccine comprises a cationic lipid. However, the Office Action alleges that it would have been obvious to combine the '473 patent with Klavinskis.

It is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicants believe that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. Applicants respectfully submit that there is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

Applicants respectfully point out that the selecting an adjuvant for a particular vaccine is per se inventive and not routine experimentation or optimization. In addition to the foregoing and the arguments of record, submitted herewith is a copy of the following articles, provided to show that one cannot extrapolate from the documents cited in the Office Action to assert that the instant invention is obvious, and to show teachings in the art away from the instant invention:

Edelman, "An Update on Vaccine Adjuvants in Clinical Trial," Aids Research and Human Retroviruses 8(8):1409-1411 (1992),

McElrath, "Selection of potent immunological adjuvants for vaccine construction," seminars in Cancer Biology 6:375-385 (1995),

Aucouturier et al., "Adjuvants designed for veterinary and human vaccines," Vaccine 19:2666-2672 (2001),

East et al., "Adjuvants for New Veterinary Vaccines," Chapter 1 in Progress in Vaccinology, vol. 4 Veterinary Vaccines, Springer Verlag, NY 1993, pp1-28,

Altman et al., "Immunomodifiers in Vaccines," Advances In Veterinary Science and Comparative Medicine 33:301-343 (1989), and

Wiilson et al., "Tissue Reaction and Immunity in Swine Immunized with *Actinobacillus pleuropneumoniae* Vaccines," Can J Vet Res 59:299-305 (1995).

The Examiner is respectfully requested to consider and make of record the herewith submitted articles, which are also cited on PTO-1449.

Edelman teaches that adjuvant use remains largely empiric. Edelman also teaches that adjuvant effects are unpredictable, with adjuvant results arising from a complex interplay between route of administration, timing of inoculations, antigen dose, host species, and within-species genetic variation. Thus, Edelman teaches that as a consequence of these variables, antigens are best matched with adjuvants by means of a trial by error process of iterative experiments, thereby showing that the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

McElrath teaches that the success of an adjuvant in clinical studies may not always be predictable from animal studies, and that adjuvant properties may differ according to the immunogen with which the adjuvant is formulated (*See, e.g.,* Summary p 283). Thus, McElrath also shows that the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

Aucouturier teaches there is no universal adjuvants. Adjuvants must be adapted according to several criteria, such as the target species, the antigen, the type of immune response,

inter alia (abstract, conclusion), further demonstrating that the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

East provides that the mechanisms by which adjuvants promote the immune response are poorly understood. Indeed, East teaches that studies involving adjuvants still do not allow the skilled artisan to predict with confidence which adjuvant will work, particularly with recombinant vaccines, as the author directs that it is clear that, much more work needs to be done on the nature of immunopotentiation and adjuvant action before the skilled artisan can, with confidence, combine new generation antigens with appropriate adjuvants to make successful vaccines. (*See* Introduction p. 2, Conclusion, p. 17). East also shows that the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

Altman discusses the hope for a universal vaccine formulation, in terms of optimal combinations of vehicles (which includes adjuvants, *see* p313), and notes that a universal vaccine formulation will not be available in the near future. Simply, examination of the vast literature in this area reveals that for almost every vehicle (including adjuvant) found to be effective with a given antigen and a certain vaccination schedule, a contrasting report documents the lack of activity by the same immunomodifier(s) with another antigen or under slightly different conditions (Concluding remarks page 338). Accordingly, the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

And, Wiilson provides an example of trial with several adjuvants, showing that components known as an adjuvant (e.g., it has been effective as adjuvant in another setting), including the famous aluminium hydroxyde used in human vaccination, is not necessarily effective as an adjuvant in another setting (abstract), demonstrating that the extrapolation attempted in the Office Action is not consistent with the knowledge in the art, that the

extrapolation attempted in the Office Action is not proper, and, that the extrapolation attempted in the Office Action is impermissible hindsight gleaned from the instant invention.

In addition to the herein arguments and herewith literature, and the arguments of record, attention is respectfully directed to MPEP 2143.02 which provides that obviousness requires a reasonable expectation of success. As discussed herein and in the record, and through the literature herewith, there was no reasonable expectation of success of the instant invention prior to the present invention.

Furthermore, attention is respectfully directed to MPEP 2143 which mandates that the fact that references can be combined or modified is insufficient for an obviousness rejection; there must be some desirability in the art to modify reference teachings to arrive at an invention. In the present situation, as discussed herein and in the record, and through the literature herewith, there is no teaching, suggestion, incentive or motivation to modify the cited documents to arrive at the instant invention.

In addition to the nonobvious arguments presented above, Applicants also respectfully direct the Examiner to Example 17 on page 65 to 67 of PCT Publication WO 01/5288. The Examiner is respectfully requested to consider and make of record the herewith submitted PCT publication, which is also cited on PTO-1449. The data presented in Example 17 of PCT Publication WO 01/5288 presents the neutralizing antibody response of cattle immunized with plasmids expressing gB, gC and gD genes from bovine herpesvirus type-1 (BHV-1) in the presence or absence of DMRIE-DOPE. In the presence of DMRIE-DOPE, the neutralizing response is significantly higher than the neutralizing response in the absence of DMRIE-DOPE. Thus, the above data presents surpringly superior results when a DNA vaccine is administered to an animal (e.g., cattle) in the presence of a cationic lipid (e.g., DMRIE-DOPE) as compared to administration of the DNA vaccine in the absence of a cationic lipid.

Accordingly, it is respectfully submitted that when one considers all of the teachings in the art, and the mandates of the case law and the MPEP, it is clear that the obviousness-type double patenting rejection cannot stand.

Therefore, the cited documents fail to teach or suggest the instant invention. Applicants reiterate that there is no motivation to combine the '473 patent with Klavinskis. Xiang, Baker, Li and Choi do not cure the deficiencies of the '473 patent or Klavinskis. Accordingly, in view

of the herein arguments and the accompanying references, reconsideration and withdrawal of the obviousness type double patenting rejection are respectfully requested.

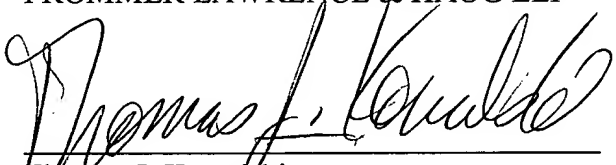
REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Office Action is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

Thomas J. Kowalski
Reg. No. 32,147
Telephone: (212) 588-0800
Facsimile: (212) 588-0500